

UTILITY PATENT APPLICATION TRANSMITTAL

(Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
ARC 2702D1Total Pages in this Submission
38**TO THE ASSISTANT COMMISSIONER FOR PATENTS**Box Patent Application
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application entitled:

PHARMACEUTICAL COATING COMPOSITION AND METHOD OF USE

and invented by:

Edgren et alIf a **CONTINUATION APPLICATION**, check appropriate box and supply the requisite information:☐ Continuation ☒ Divisional ☐ Continuation-in-part (CIP) of prior application No.: 09/129,687

Which is a:

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.:

Which is a:

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.:

Enclosed are:

Application Elements

1. ☒ Filing fee as calculated and transmitted as described below
2. ☒ Specification having 29 pages and including the following:
 - a. ☒ Descriptive Title of the Invention
 - b. ☒ Cross References to Related Applications (if applicable)
 - c. ☐ Statement Regarding Federally-sponsored Research/Development (if applicable)
 - d. ☐ Reference to Microfiche Appendix (if applicable)
 - e. ☒ Background of the Invention
 - f. ☒ Brief Summary of the Invention
 - g. ☒ Brief Description of the Drawings (if drawings filed)
 - h. ☒ Detailed Description
 - i. ☒ Claim(s) as Classified Below
 - j. ☒ Abstract of the Disclosure

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Application Elements (Continued)

3. ☒ Drawing(s) *(when necessary as prescribed by 35 USC 113)*
- a. ☐ Formal Number of Sheets _____
- b. ☒ Informal Number of Sheets 4
4. ☒ Oath or Declaration
- a. ☐ Newly executed *(original or copy)* ☐ Unexecuted
- b. ☒ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*
- c. ☒ With Power of Attorney ☐ Without Power of Attorney
- d. ☐ DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) named in the prior application,
see 37 C.F.R. 1.63(d)(2) and 1.33(b).
5. ☐ Incorporation By Reference *(usable if Box 4b is checked)*
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under
Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby
incorporated by reference therein.
6. ☐ Computer Program in Microfiche *(Appendix)*
7. ☐ Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all must be included)*
- a. ☐ Paper Copy
- b. ☐ Computer Readable Copy *(identical to computer copy)*
- c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

8. ☐ Assignment Papers *(cover sheet & document(s))*
9. ☐ 37 CFR 3.73(B) Statement *(when there is an assignee)*
10. ☐ English Translation Document *(if applicable)*
11. ☐ Information Disclosure Statement/PTO-1449 ☐ Copies of IDS Citations
12. ☒ Preliminary Amendment
13. ☒ Acknowledgment postcard
14. ☒ Certificate of Mailing
- ☐ First Class ☒ Express Mail *(Specify Label No.):* EL523936116US

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38

Accompanying Application Parts (Continued)

15. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed)

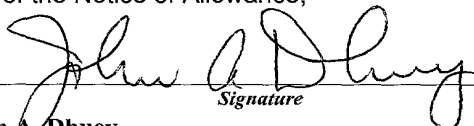
16. ☐ Additional Enclosures (please identify below):

Fee Calculation and Transmittal

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra	Rate	Fee
Total Claims	4	- 20 =	0	x \$18.00	\$0.00
Indep. Claims	4	- 3 =	1	x \$78.00	\$78.00
Multiple Dependent Claims (check if applicable) <input type="checkbox"/>					\$0.00
BASIC FEE					\$690.00
OTHER FEE (specify purpose)					\$0.00
TOTAL FILING FEE					\$768.00

- ☐ A check in the amount of _____ to cover the filing fee is enclosed.
- ☒ The Commissioner is hereby authorized to charge and credit Deposit Account No. **01-1173** as described below. A duplicate copy of this sheet is enclosed.
- ☒ Charge the amount of **\$768.00** as filing fee.
- ☒ Credit any overpayment.
- ☒ Charge any additional filing fees required under 37 C.F.R. 1.16 and 1.17.
- ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).


Signature

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Dated: 11-22-00

cc:

11-24-00

A

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10)

Applicant(s): Edgren et al

Docket No.

ARC 2702D1

Serial No.

Filing Date

Examiner

Group Art Unit

Inventor: PHARMACEUTICAL COATING COMPOSITION AND METHOD OF USE

Certificate of Mailing by Express Mail;
Utility Patent Application Transmittal;
Copy of Regular Patent Application including drawings;
Copy of Declaration and Power of Attorney;
Preliminary Amendment; Postcard for return.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Edgren et al

Serial No.:

Group Art Unit:

Filed: Herewith

Examiner:

For: Pharmaceutical Coating
Composition and Method
of Use

Preliminary Amendment

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir/Madam:

PRELIMINARY AMENDMENT

Please amend the above-identified application filed herewith as follows:

IN THE SPECIFICATION

In the first paragraph on the first page, line 5, after "This application" add – is a division of Application Serial No. 09/129,687 filed August 5, 1998, which --.


IN THE CLAIMS

In claim 2, line 2, before "cellulose triacylate" insert – and --; and in line 3 delete "and ethyl cellulose".

Early passage to issue of the present application is solicited.

Respectfully submitted,

Dated: 11-22-00


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PHARMACEUTICAL COATING COMPOSITION AND METHOD OF USE**CROSS-REFERENCE TO RELATED APPLICATION**

This application claims the benefits of provisional application U.S. Serial No. 60/058,264 filed September 9, 1997 under 35 U.S.C. §119(e).

FIELD OF THE INVENTION

This invention pertains to a novel and useful pharmaceutical coating composition. More particularly, the invention related to a pharmaceutically acceptable composition comprising at least one polymer and at least one surfactant which composition with a single solvent can be coated onto a dosage form. The invention concerns also a process of coating a dosage form with the composition and the solvent.

BACKGROUND OF THE INVENTION

In Remington's Pharmaceutical Sciences, 14th, Ed., p 1681, published in 1970, it was reported that pill coating has been a pharmaceutical technique for well over ten centuries. For example, Rhazes (850-932 A.D.) used mucilage, a seaweed substance, for coating pills in the ninth century, and Avicenna (980-1037 A.D.) is credited with the introduction of silver and gold pill coatings into medicine. The coating of pills with finely powdered talcum, called pearl coating, was popular in previous times. Gelatin coating of pills was introduced into medicine by Garot in 1838. The first sugar-coated pills in the United States were imported from France in about 1842. The first sugar-coated pill was manufactured in the United States in 1856 by Warner, a Philadelphia pharmacist. In about 1884 Unna introduced enteric coated pills.

1 Unique pharmaceutically-acceptable tablets, manufactured as an
2 osmotic dosage form entered the fields of medicine and pharmacy with the
3 invention of osmotic dosage forms by inventors Theeuwes and Higuchi in
4 U. S. Patent Nos. 3,845,770 and 3,916,899. The osmotic dosage forms
5 disclosed in these patents comprise a semipermeable membrane that
6 surrounds a compartment containing a therapeutic agent. The membrane is
7 permeable to the passage of an external fluid, and it is impermeable to the
8 passage of drug. There is at least one exit through the membrane for
9 delivering the therapeutic agent from the osmotic dosage form.

10 A pioneering advancement in osmotic dosage forms was made
11 available to the drug dispensing arts in U. S. Patent No. 4,327,725 by
12 patentees Cortese and Theeuwes. The invention provided by these inventors
13 concerned an osmotic dosage form for delivering a therapeutic agent, that
14 because of its solubility, is difficult to deliver in therapeutic amounts at a
15 controlled rate over time. The dosage form of U. S. Patent No. 4,327,725
16 comprises a semipermeable wall that surrounds a therapeutic agent and an
17 expandable agent. In operation, the expandable agent in the presence of
18 imbibed fluid, expands and pushes the therapeutic agent through an exit
19 passageway from the dosage form.

20 While the above presented dosage forms are useful for the
21 management of health and disease, a serious disadvantage is associated
22 with their manufacture. That is, the prior art used two or more solvents to
23 dissolve a coating-forming membrane and a flux enhancer, because one
24 solvent does not dissolve both the membrane and the flux enhancer. A
25 typical solvent system used by the prior art for this purpose comprises two or
26 more organic solvents, often possessing degrees of unknown incompatibility.
27 Further, the prior art solvents often produced high-flux membranes that
28 exhibited mechanical defects, which lead to weakened membranes
29 accompanied by brittleness. Then too, the use of multiple solvent can
30 produce haziness or opacity in a membrane, which makes it impossible to

1 identify selected regions of a dosage form. Also, the use of multiple organic
2 solvents presents an environmental problem as the solvents require
3 complicated recover systems to avoid contaminating the environment, which
4 recovery systems are expensive to install and to operate.

5 It will be appreciated by those skilled in the drug dispensing art, that if
6 a coating is provided that comprises a single solvent and its substantively-free
7 of excessive organic solvent for coating dosage forms, such a coating and its
8 accompanying solvent would have an immediate positive value, and
9 concomitantly, represent an advancement in the drug coat and drug coating
10 art. Likewise, it will be appreciated by those versed in the coat and process-
11 coating arts, that if a coat and a process for coating are made available for
12 dosage forms that overcome the disadvantages known to the prior art, they
13 would have a practical application in the fields of medicine and pharmacy.

14 15 16 OBJECTS OF THE INVENTION

17
18 Accordingly, in view of the above presentation, it is an immediate
19 object of this invention to provide a novel and useful coating composition for
20 dosage forms, and which coating composition overcomes the disadvantages
21 associated with the prior art.

22 Another object of this invention is to provide a new coating composition
23 comprising pharmaceutically acceptable ingredients, and which coating
24 composition is innocuous and useful for manufacturing a dosage form.

25 Another object of this invention is to provide a nontoxic coating
26 composition, which coating composition is useful for making dosage forms.

27 Another object of this invention is to provide a coating composition
28 comprising a membrane and a surfactant, which coating composition is
29 capable of being applied to a dosage form without difficulty and is applied at
30 relative lower cost.

1 Another object of this invention is to provide a composition comprising
2 a membrane and a surfactant, and a common solvent for the membrane and
3 the surfactant.

4 Another object of the invention is to provide a coating composition
5 characterized by simplicity of formulation, ease of manufacture and a single
6 solvent system that can be use to form a coating solution that avoids binary or
7 tertiary solvent systems.

8 Other objects, features and advantages of this invention, will be more
9 apparent to those versed in the dispensing art from the following detailed
10 specification taken in conjunction with the drawings and the accompanied
11 claims.

12 **BRIEF DESCRIPTION OF THE DRAWINGS**

13
14
15 In the drawing figures, which are not drawn to scale, but are set forth to
16 illustrate various embodiments of the inventory, the drawing figures are as
17 follows:

18
19 Drawing Figure 1 depicts the release rate vs the reciprocal membrane
20 weight for two coating conditions.

21 Drawing Figure 2 depicts the release rate vs the reciprocal membrane
22 weight sprayed from two ethanol/water ratios.

23 Drawing Figure 3 depicts a membrane surfactant composition coated
24 from a single solvent from three coating runs.

25 Drawing Figure 4 depicts membranes coated from a binary solvent
26 from four coating runs.

27 In the drawing figures and in the specification, like parts in related
28 figures are identified by like numbers. The terms appearing earlier in the
29 specification and in the description of the drawing figures, as well as in
30 embodiments thereof, are further described elsewhere in this disclosure.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the practice of this invention, a therapeutic agent, including a drug, is coated with a composition comprising a polymer and a surfactant. The polymer in the process of coating the therapeutic agent converts to a membrane that surrounds the therapeutic agent to yield a dosage form. The polymer is nontoxic, and it does not adversely affect an animal host, including a human, and a therapeutically-acceptable drug. The polymers useful for providing a membrane comprise a member selected from the group consisting of cellulose ester, cellulose ether, and cellulose ester-ether. Representative of specific polymers comprise a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, and cellulose triacetate, and ethylcellulose. The amount of polymer on a weight based in a coating composition in a final, dry coated membrane is 40 wt % to 99.5 wt %.

In coating composition comprising the polymer also comprises one or more pharmaceutically acceptable surfactants. The surfactant generally for the purpose of this invention is amphiphilic as it contains both a hydrophobic and a hydrophilic group. Representative of surfactants that exhibit solubility in aqueous and nonaqueous solvents are polyoxyethylene fatty acid esters that includes polyoxyethylene monostearate, polyoxyethylene sorbitan monopalmitate, polyoxypropylene glycols that include polyoxypropylene glycol having a molecular weight of 950 and 3 moles to 85 moles of ethylene oxide, polyoxypropylene glycol possessing a molecular weight of 1200 and 7 to 40 moles of ethylene glycol, polyoxypropylene glycol possessing a mole weight of 1750 and 5 moles to 160 moles of ethylene oxide, polyoxypropylene glycol having a molecular weight of 2050 and 10 moles to 110 moles of ethylene oxide, polyoxypropylene glycol having a 2250 molecular weight and 5 moles to 200 moles of ethylene oxide, polyoxypropylene glycol possessing a molecular weight of 2750 and 15 to 250 moles of ethylene oxide, and

polyoxypropylene glycol of 3250 molecular weight and 8 moles to 300 moles of ethylene glycol. The amount of surfactant in a composition for coating is 0.5 wt % to 60 wt %.

Other pharmaceutically acceptable surfactants for the purpose of this invention include triblock copolymers of ethylene oxide-propylene oxide, ethylene oxide, which include polymers with an average molecular weight of 2200 and 3 to 20 moles of ethylene oxide, polymers with molecular weight 8,600 and 50 to 110 moles of ethylene oxide, polymers with molecular weight of 7800 and 45 to 80 moles of ethylene oxide, polymers with 15,000 molecular weight and 110 to 170 moles of ethylene oxide, and those with molecular weight 12,200 and 70 to 130 moles of ethylene oxide.

Other pharmaceutically acceptable surfactants suitable for use in this invention include monoglycerides, diglycerides, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene sorbitol esters, polyoxyethylene esters of acids, polyoxyethylene alcohols, polyoxyethylene glyceride ester, polyoxyethylene-oxypropylene monostearate with 10 to 40 moles of ethylene oxide, polyoxyethylene alkyl amine, ionic surfactants such as N-cetyl-ethyl morpholinium ethosulfate, N-soya-n-ethyl morpholinium ethosulfate, alkyl aryl sulfonate, polyoxyethylene ether, polyoxyethylene glyceride alkyl aryl sulfonate blend, polyoxyethylene alkyl aryl ether-alkyl aryl sulfonate blend, nonionic-anionic blends, and polyethylene sorbitol oleate-polyoxyethylene amine blend.

The composition for providing the coating composition comprises of 0 wt % to 30 wt % of a surfactant polymer of hydroxypropylcellulose of 7,500 to 150,000 weight average molecular weight, and 0 wt % to 30 wt % of a polyvinylpyrrolidone of 1,200 to 225,000 viscosity average molecular weight. A coloring agent, a colorant, or opacifying agent can be added to the composition to identify the dosage form. The colorant should be pharmaceutically acceptable as represented by FD & C Red No. 3, FD & C Red No. 40, FD & C Yellow No. 5, FD & C Yellow No. 6, FD & C Blue No. 1,

1 FD & C Blue No. 2, FD & C Green No. 5, and iron oxides including black,
2 yellow and red iron oxides. The opacifying agent should be pharmaceutically
3 acceptable such as finely-divided titanium dioxide. The amount of colorant or
4 opacifying agent in a composition is 0 wt % to 3.5 wt %.

5 Optionally, other functional excipients can be formulated within the
6 coating composition such as anti-tack agents to improve coating quality and
7 ease of processing. Anti-tack agents can be incorporated within the coating
8 single-solvent composition in dissolved form or in the dispersed form. Anti-
9 tack agents are formulated at zero to five weight percent based on the drug
10 weight of the coating composition. These agents include glycerol fatty acid
11 esters such as glycerol monostearate, fats of glycerides of saturated C12 to
12 C18 fatty acids, esters of medium chain fatty acids such as, coconut oil, palm
13 kernal oil, babassu oil, finely divided silicon dioxide, silica aluminates, talc,
14 precipitated silicas, fumed silicas, metal fatty acids such as magnesium
15 stearate, fatty acids saturated C12 to C18 such as stearic acids, and
16 saturated C12 to C18 alcohol such as stearyl alcohol.

17 The dosage form, when manufactured as an osmotic dosage form with
18 controlled-release properties comprises at least one exit in the dosage form
19 membrane. The phase controlled-release as used herein, indicates that
20 control is exercised over both the duration and the profile of the drug-release
21 pattern. The expression passageway, as used for the purpose of this
22 invention, includes aperture, orifice, bore, pore, porous element through
23 which the drug can be pumped, diffuse, travel or migrate, a hollow fiber,
24 capillary tube, porous overlay, porous insert, microporous member, and
25 porous composition. The expression also includes a compound that erodes
26 or is leached from the membrane in the fluid environment of use to produce at
27 least one passageway in dosage form. Representative compounds suitable
28 for forming at least one passageway, or a multiplicity of passageways,
29 includes an erodible poly(glycolic) acid or poly(lactic) acid member in the wall;
30 a gelatinous filament; a water-removable poly(vinyl alcohol); leachable

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1 compounds such as fluid removable pore-forming polysaccharides, acid,
2 salts, or oxides. A passageway or a plurality of passageways can be formed
3 by a leaching a compound such as sorbitol, sucrose, lactose, fructose, or the
4 like, from the membrane to provide a controlled-release dimensioned pore-
5 passageway. The passageway can have any shape such as round,
6 triangular, square, elliptical, and the like, for assisting in the controlled-
7 metered release of drug from dosage form. Dosage form can be constructed
8 with one or passageways in spaced apart relation to one or more surfaces of
9 a dosage form. Passageway and equipment for forming passageways are
10 disclosed in U.S. Patent Nos. 3,845,770 and 3,916,899 by Theeuwes and
11 Higuchi; in U.S. Patent No. 4,063,064 by Saunders et al.; and in U.S. Patent
12 No. 4,088,864 by Theeuwes et al. Passageways comprising controlled
13 releasing dimension, sized, shaped and adapted as a releasing-pore formed
14 by aqueous leaching to provide a releasing-pore formed by aqueous leaching
15 to provide a releasing-pore of controlled release-rate are disclosed in U.S.
16 Patent No. 4,200,098 by Ayer and Theeuwes; and in U.S. Patent No.
17 4,285,987 by Ayer and Theeuwes.

18 The membrane is manufactured and applied in one process,
19 comprises an air suspension process. This procedure consists in suspending
20 and tumbling a compressed drug core comprising a single layer or a bilayer
21 core, in a current of air and wall forming composition until a wall is applied to
22 the core. The air suspension procedure is well-suited for independently
23 forming the wall. The air suspension procedure is described in U.S. Patent
24 2,799,241; *J. A. Pharm. Assoc.*, Volume 48, pages 451 to 454, (1959); and
25 *ibid*, Volume 49, pages 82 to 84, (1960).

26 The dosage form can be coated in an air suspension coat, or by other
27 membrane forming techniques such as pan-coating systems, wherein
28 membrane forming compositions are deposited by successive spraying of the
29 composition on the drug-core compartment, accompanied by tumbling in a
30 rotating pan. Finally, the membrane coated compartments are dried in a

1 forced air over at 30° C to 50° C for up to a week to free dosage form 10 of
2 solvent. Generally, the membrane formed by these techniques have a
3 thickness of 1 to 30 mils (0.254 mm to 0.762 mm, with a presently preferred
4 thickness of 4 to 10 mils, 0.101 mm to 0.254 mm).

5 The dosage form of the invention is manufactured by standard
6 manufacturing techniques. For example, in one manufacture the drug and
7 other core-forming ingredients comprising a single drug layer or bilayer core
8 facing the exit means are blended and pressed into a solid layer, or a solid
9 bilayer. The drug and other ingredients can be dry-blended or blended with a
10 solvent and mixed into a solid or semisolid formed by conventional methods
11 such as ball-milling, calendaring, stirring, roll-milling or churning and then
12 pressed into a preselected shape. The layer possesses dimensions that
13 correspond to the internal dimensions of the area the layer is to occupy in the
14 dosage form and in a bilayer it also possesses dimensions corresponding to
15 the second layer for forming a contracting arrangement therewith. Next, in a
16 bilayer core, the push layer is placed in contact with the drug layer. The push
17 layer is manufactured using techniques for providing the drug layer. The
18 layering of the drug layer and the push layer can be fabricated by convention
19 press-layering techniques. Finally, a single layer or the two layer
20 compartment, the layer or layers are surrounded with a membrane. A
21 passageway is laser, leached, or mechanically drilled through the membrane
22 to contact the drug layer. When the passageway is formed by a laser, the
23 dosage form is optically-oriented automatically by the laser equipment for
24 forming the passageway on the preselected surface for forming the
25 passageway.

26 In another manufacture, the dosage form is manufactured by the wet
27 granulation technique. In the wet granulation technique, for example, the
28 drug and the ingredients comprising the drug-forming layer are blended using
29 a solvent, such as ethyl alcohol-water 98:2 v:v (volume:volume) as the
30 granulation fluid. Other granulating fluid, such as denatured alcohol 100%,

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1 can be used for this purpose. The ingredients forming the drug layer are
2 individually passed through a 20 mesh screen and then thoroughly blended in
3 a mixer. Next, other ingredients comprising the drug layer are dissolved in a
4 portion of the granulation fluid, such as the cosolvent described above. Then,
5 the latter prepared wet blend is slowly added to the drug blend with continual
6 mixing in the blender. The granulating fluid is added until a wet blend is
7 produced, which wet mass than is forced through a 20 mesh screen onto
8 oven trays. The blend is dried for 18 to 24 hours at 30°C to 50°C. The dry
9 granules are sized then with a 20 mesh screen. Next, a lubricant is passed
10 through screen, such as a 80-mesh screen, and added to the dry screen
11 granule blend. The granulation is placed in a blender and blended for 1 to 15
12 minutes. A push layer is made by the same wet granulation techniques. The
13 compositions are pressed into their individual layers in a layer press.

14 Another manufacturing process that can be used for providing the
15 compartment-forming composition layers comprises blending the powdered
16 ingredients for each layer independently in a fluid bed granulator. After the
17 powdered are dry blended in the granulator, a granulating fluid, for example,
18 poly(vinylpyrrolidone) in water, or in denatured alcohol, is sprayed on the
19 powders. Optionally, the ingredients can be dissolved or suspended in the
20 granulating fluid. The coated powders are then dried in a granulator. This
21 process granulated all the ingredients present therein while added the
22 granulating fluid. After the granules are dried, a lubricant such as stearic acid
23 or magnesium stearate is added to the granulator. The granules for each
24 separate layer are pressed then in the manner described above.

25 The dosage form of the invention can be manufactured by mixing a
26 drug with composition-forming ingredients and pressing the composition into
27 a layer possessing dimensions that correspond to the internal dimensions of
28 the compartment of the dosage form. In another manufacture the drug and
29 other drug composition-forming ingredients and a solvent are mixed into a
30 solid, or a semisolid, by conventional methods such as ballmilling, shaking,

1 calendaring, tumbling, stirring or rollmilling, and then pressed into a
2 preselected layer-forming shape. Next, a layer of a composition comprising
3 an osmopolymer and an optional osmagent are placed in contact the drug
4 layer. The layering of the first layer comprising the drug and the second layer
5 comprising the osmopolymer and optional osmagent composition can be
6 accomplished by using a conventional layer press technique. The wall can be
7 applied by molding, brushing, spraying or dipping the pressed bilayer's
8 shapes with all-forming materials. another and preferred technique that can
9 be used for applying the wall is the air-suspension coating procedure. This
10 procedure consists in suspending and tumbling the two contacting layers in
11 current of air until the wall-forming composition surrounds the layers. The air
12 suspension procedure is described in U.S. Pat. No. 2,799,241; *J. Am. Pharm.*
13 *Assoc.*, Vol. 48 pp 451-454 (1979); and, abid, Vol. 49, pp 82-84 (1960).
14 Other standard manufacturing procedures are described in *Modern Plastics*
15 *Encyclopedia*, Vol. 46, pp 62-70 (1969); and in *Pharmaceutical Science*, by
16 Remington, 14th Ed., pp 1626-1678 (1970), published by Mack Publishing
17 Co., Easton, Pa.

18 Exemplary solvents suitable for manufacturing the wall, a single layer
19 and a bilayer core include inert inorganic and organic solvents final laminated
20 wall. The solvents broadly include a single solvent members selected for the
21 group consisting of aqueous solvent, alcohol, ketone, ester, ether, aliphatic
22 hydrocarbon, halogenated solvent, cyclaliphatic, aromatic, and heterocyclic
23 solvents. Typical solvents include acetone, diacetone, alcohol, methanol,
24 ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate,
25 isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl
26 ketone, n-hexane, n-heptane ethylene glycol monoethyl ether, ethylene glycol
27 monoethyl acetate, methylene dichloride, ethylene dichloride, propylene
28 dichloride, carbon tetrachloride, chloroform, nitroethane, nitropropane,
29 tetrachoroethan, ethyl ether, isopropyl ether, cyclohexane, cyclooctane,
30 benzene, toluene, naptha, tetrahydrofuran, and diglyme.

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1 The expression therapeutically active agent as used for the purposes
2 of this invention includes a drug, or a composition comprising a
3 therapeutically active drug and other composition forming ingredients the term
4 drug includes any physiologically or pharmacologically active substance that
5 produces a local or a systemic effect in animals including humans. The terms
6 physiologically and pharmacologically are defined in Stedman's Medical
7 Dictionary, published by Williams and Wilkins, 1966, Baltimore, MD. The drug
8 comprise a member selected from the group consisting of anticonvulsant,
9 analgesic, anti-inflammatory, anesthetic, anti-Parkinson, antimicrobial,
10 antimalarial, antiviral, antiparasitic, cardiovascular, contraceptive, central
11 nervous system actant including depressant and stimulant, diuretic,
12 electrolyte, hormone, hypoglycemic, muscle contractant, muscle relaxant,
13 hypnotic, ophthalmic, psychic energizer, neoplastic, sedative,
14 sympathomimetic, and tranquilizer. The drugs are known in Pharmaceutical
15 Sciences, by Remington, 17th Edition, 1985, published by Mack Publishing
16 Co., Easton, PA.

17 The drug can be in various pharmaceutically acceptable form, such as
18 uncharged molecules, molecular complexes, pharmacologically acceptable
19 salts such as hydrochloride, hydrobromide, sulfate, laurylate, palmitate,
20 phosphate, nitrate, borate, acetate, maleate, tartrate, oleate and salicylate.
21 For acidic medicines salts of metals, amines organic cations; for example
22 quaternary ammonium can be used. Derivatives of medicines, such as an
23 ester, ether and amides, can be used. Also, a medicine that is water
24 insoluble can be used in a form that is a water soluble derivative thereof to
25 serve as a solute, and its release from a dosage form it is converted by
26 enzymes, hydrolyzed by the body pH, or other metabolic process to the
27 original biologically active form.

28 Representative of drug that can be administered by this invention
29 include a member selected from the group consisting of simvastatin
30 sumatriptan, doxazosin, amlodipine, azithromycin, lisinopril, finasteride,

ziprasidone, olanzapine, risperidone, sildenafil, dofetilide, donepezil, atorvastatin, trovafloxacin, eprosartan, losartan, tasosartan, enalapril, sertindole, quetiapine, nelfinavin, ritonavir, indinavir, dexlenfluramine, and citicolene, The dose of drug in a dosage form provided by the invention is 100 micrograms to 1000 milligrams.

DETAILED DESCRIPTION OF EXAMPLES OF THE INVENTION

The following examples are merely illustrative of the present invention and they should not be considered as limiting the scope of the invention in any way, as these examples and other equivalents thereof will become more apparent to those skilled in the drug delivery art in the light of the present disclosure, the drawings and the accompanying claims.

EXAMPLE 1

A series of osmotic therapeutic compositions comprising a dose of pentoxifylline were coated with a membrane-forming composition comprising 55 wt % of ethylcellulose having an ethoxyl content of 48.0 to 49.5 weight percent and a 220,000 molecular weight, 20 wt % of hydroxypropylcellulose of 60,000 molecular weight, 20 wt % of polyvinylpyrrolidone of 1,300 molecular weight and 5 wt % of polyoxyethylenated stearate comprising 40 moles of ethylene oxide. The wall-forming ingredients were dissolved with stirring in 100% anhydrous ethanol. Then, the freshly prepared coating solution was allowed to solvate as room temperature, 20°C, for 72 hours. The solvated solution was divided into two equal portions. One portion was spray coated on the therapeutic compositions without stirring the solution, and the other portion was stirred continuously while the coating was applied to the therapeutic composition. The performance curves of the resulting dosage forms were equivalent as seen in Figure 1. Drawing Figure 1 illustrates the

1 release rate vs the reciprocal membrane weight for dosage forms sprayed at
2 two coating conditions. The clear square indicates membranes formed
3 unstirred while spraying and the dark squares indicates membranes formed
4 while spraying the membrane forming composition. The core of the dosage
5 form comprised a bilayer tablet therapeutic composition. One layer, the drug
6 layer, weighed 845 mg and consisted of 71 wt % pentoxifylline, 24.67 wt %
7 polyethylene oxide of 200,000 molecular weight, 4 wt % polyvinylpyrrolidone
8 of 40,000 molecular weight, 0.25 wt % magnesium stearate and 0.08 wt %
9 butylated hydroxytoluene. The dosage form comprises a push layer
10 composition for pushing the therapeutic composition from the dosage form.
11 The push layer composition weighed 200 mg and consists of 97.70 wt %
12 polyethylene oxide of 5,000,000 molecular weight, 1 wt %
13 polyvinylpyrrolidone of 40,000 molecular weight, 1 wt % ferric oxide, 0.25 wt
14 % magnesium stearate, and 0.05 wt % butylated hydroxyltoluene. The
15 membrane comprises two round 25 mil (0.635 mm) diameter exits.

16 17 EXAMPLE 2

18 A series of therapeutic compositions were prepared for manufacturing
19 into dosage forms for illustrating the unexpected improvements for the
20 dosage forms of Example 1 over the dosage forms of Example 2. In Example
21 2, therapeutic compositions comprising pentoxifyllene were coated with a
22 membrane composition comprising 55 wt % ethylcellulose of 220,000
23 molecular weight, 22.5 wt % hydroxypropylcellulose of 60,000 molecular
24 weight and 22.5 wt % of polyethylene glycol of 8,000 molecular weight. The
25 membrane was coated with a binary solvent system consisting of 3,477 ml of
26 anhydrous ethanol and 47 ml of water. The membrane coating solution was
27 prepared by dissolving the ethylcellulose and the hydroxypropylcellulose in
28 the ethanol and the polyethylene glycol in water and then blending the two
29 solutions to form the final coating solution. The polyethylene glycol was
30 soluble in water and in the ethanol binary mixture, but not soluble in ethanol

1 alone. The final coating solution comprised 98.3% ethanol and 1.7% water.
2 A subsequent coating composition comprised 95% ethanol and 5% water.
3 The two coating runs produced dosage form comprising membrane of distinct
4 coating weights. The results of the measured performance of individual
5 membrane dosage forms for two coating revealed the membranes which
6 were formed with the coating revealed the membranes which were formed
7 with the coating solutions having 5% water produced much faster release rate
8 of drug than membranes of comparable weight coated with 1.7% water as
9 seen in drawing Figure 2. The wide divergence of these two performance
10 curves demonstrated that small changes in the ratio of a binary solvent can
11 produce significantly different permeabilities in membranes. For this binary
12 system it makes the production of reproducible membrane very different
13 because it is difficult to keep the ratio of solvents constant from batch to batch
14 and from within a batch during the coating process.

15 The accompanying drawing Figure 2 illustrates the release rate vs
16 reciprocal membrane weight for a series of dosage forms comprising
17 ethylcellulose in the membrane. In the drawing Figure 2, the clear circles
18 represent a binary solvent comprising 95% ethanol and 5% water and the
19 clear squares represent a binary solvent system comprising 98.3% ethanol
20 and 1.7% water. The dosage form of Example 2, comprises a therapeutic
21 composition weighing 845 mg and consisting of 71% pentoxifylline, 24.67
22 wt % polyethylene oxide of 200,000 molecular weight, 4 wt % polyvinyl-
23 pyrrolidone of 40,000 molecular weight, 0.25 wt % magnesium stearate and
24 0.08 wt % butylated hydroxytoluene. The dosage form comprises a push
25 composition in laminated arrangement with the therapeutic composition. The
26 push composition weigh 200 mg and comprises 97.70 wt % polyethylene
27 oxide of 5,000,000 molecular weight, 1 wt % polyvinylpyrrolidone of 40,000
28 molecular weight, 1 wt % ferric oxide, 0.25 wt % magnesium stearate, and
29 0.05 wt % butylated hydroxytoluene. The release rate form the dosage forms
30 were measured in artificial gastric juice at 37° C. The dosage form comprised

two, 25 mil (0.635 mm) exit passageways in the membrane that connected the therapeutic composition with the exterior of the dosage form.

EXAMPLE 3

The procedure of Example 1 is followed in this example. In this example, the therapeutic composition is coated with a membrane composition consisting of 79 wt % cellulose acetate comprising 39.8% acetyl content having molecular weight of 40,000 and 21 wt % of a surfactant comprising 30 wt % polyoxypropylene glycol having a 8,400 molecular weight and 160 moles of ethylene oxide. The coating solution was prepared by dissolving the cellulose acetate and polyoxypropylene glycol in the single solvent with stirring and slight warming to 30°C. The membrane was sprayed from a single solvent consisting of 100% acetone, and the membranes formed from the coating composition was smooth, without cracks or cusps. The uniform morphology for these dosage forms is seen in accompanying drawing Figure 3 showing the performance of the membrane coating. Drawing Figure 3 depicts the results for a drug composition weighing 319 mg consisting of 35 % tacrine hydrochloride, 57 wt % mannitol, 3 wt % hydroxypropylmethyl-cellulose of 9,200 molecular weight, 1 wt % polyvinylpyrrolidone of 40,000 molecular weight, 3 wt % crosslinked polyvinylpyrrolidone, 1 wt % magnesium stearate which composition is surrounded by the membrane. The dosage form comprises two 10 ml (0.254 mm) exit passageways for releasing the drug from the dosage form. In drawing Figure 3, the clear circles, triangles and squares depict the release pattern for these lots of dosage forms, with each symbol type representing each of three lots. The figure illustrates the data is clustered together, indicating good reproducibility. The morphology of the membranes when observed in cross section under microscopic examination was smooth, without cracks, laminations, striations, or cusps.

EXAMPLE 4

Therapeutic compositions comprising tacrine hydrochloride were coated with a membrane-forming composition comprising 75 wt % cellulose acetate comprising a 39.8% acetyl content and having a molecular weight of 40,000, 23 wt % polyvinylpyrrolidone and having a molecular weight of 40,000, and 2 wt % triethylcitrate. The membrane-forming ingredients were dissolved in a binary solvent comprising 80/20 (wt/wt) acetone/methanol. The therapeutic compositions were coated with the membrane and the performance is depicted in drawing Figure 4. In drawing Figure 4, the drug composition coated with the membrane weighed 321.3 mg, and consisted of 34 wt % tacrine hydrochloride, 60 wt % mannitol, 3 wt % hydroxypropylmethyl-cellulose of 9, 200 molecular weight, 1 wt % polyvinylpyrrolidone of 40,000 molecular weight, 1 wt % cross-linked sodium carboxymethylcellulose, and 1 wt % magnesium stearate. The dosage form comprises two 10 mil (0.254 mm) exit orifices. In drawing Figure 4, the clear circles, triangles, squares and diamonds illustrate different dosage forms release rate analyzed with 10 dosage forms in each of four lots. Each type of symbol represents one lot. Figure 4 depicts the dosage forms prepared by using the binary solvent exhibited unacceptable performance as the reproducibility was poor. The morphology of the membranes under microscopic examination evidence ranged from homogenous to very heterogenous. The heterogenous structures were characterized as being laminar, with striations, cracks, and cusps within the membrane structure.

EXAMPLE 5

In this example, ten surfactant flux enhancers were evaluated by coating 70/30 cellulose acetate/enhancer blends from 100% acetone. The permeability values of the surfactant enhancer are summarized in Table 1. The Pluronic F68 compound produced the highest permeability value. It also

produced membranes which had the most uniform morphology when examined in cross section under microscopic examination.

Samples of the membrane were soaked from coated cores and tested for tensile properties. A miniature dogbone shaped steel rule die was used to punch out samples for testing. The dogbone-shaped samples were pulled on tensile tester. The modulus of elasticity, elongation at break, and toughness values for the 70/30 cellulose acetate/Pluronic F68 membrane were high; 59 kgf/mm², 23%, and 0.3 kgf/mm², respectively.

Therefore, this membrane which was formulated with a surfactant flux enhancer and sprayed from a single solvent had a high water permeability value, had good mechanical properties, and was reproducible.

TABLE 1

Surfactant Enhancer	Melting Point (°C)	Mol. Wt (g/mole)	Permeability ($k \times 10^4$) (cm.mil/atm.hr)
Myrj 52S	38	2,047	10.7
Myrj 53	42	2,487	13.2
Tween 20	<25	1,126	9.3
Tween 40	13	1,282	6.5
Tween 80	<25	1,309	6.2
Luviskol VA37E	67(T _g)	45,000	2.2
Luviskol VA64P	106(T _g)	44,000	7.1
Pluronic F68	52	8,600	15.4
Pluronic F108	57	14,600	12.3
Pluronic F127	56	12,600	10.5

In Table 1, Myrj[®] 52s denoted polyoxyethylenated stearic acid with 40 moles of ethylene oxide; Myrj[®] 53 denotes polyoxyethylenated stearic acid with 50 moles of ethylene oxides; Tween[®] 20 denotes polyoxyethylenated sorbitan monolaurate with 20 moles of ethylene oxide; Tween[®] 40 denoted polyoxyethylenated sorbitan monopalmitate with 20 moles of ethylene oxide;

1 Tween® 80 denotes polyoxyethylenated sorbitan monoleate and 20 moles of
2 ethylene oxide; Luviskol® VA 37E denotes vinylpyrrolidone/vinyl acetate
3 copolymer with 30 wt % of vinylpyrrolidone and 70 wt % of vinylacetate;
4 Luviskol® VA 64P denotes vinylpyrrolidone/vinyl acetate copolymer with 60 wt
5 % vinylpyrrolidone and 40% vinyl acetate having a molecular weight of
6 approximately 60,000; Pluronic® F68 denotes polyoxypropylene glycol of
7 8,600 molecular weight and 160 moles of ethylene oxide; Pluronic® 108
8 denotes polyoxypropylene glycol of 14,600 molecular weight and 280 moles
9 of ethylene oxide; and Pluronic® 127 denotes polyoxypropylene glycol of
10 12,600 molecular weight and 200 moles of ethylene oxide. The Myrij and
11 Tween products are commercially available from the ICI Americas, Inc.,
12 Wilmington, Delaware. The Pluronic and Luviskol products are available from
13 BASF Corporation, Mt. Olive, New Jersey.

14 In as much as the foregoing specification comprises present
15 embodiments of the invention, it is understood, variations and modifications
16 can be made, in accordance with the disclosed invention, without departing
17 from the scope of the invention.

1 We Claim:

2

3 1. A composition comprising a polymer for providing a polymer
4 membrane, at least one pharmaceutically acceptable surfactant compatible
5 with the polymer, and a single solvent for both the polymer and the surfactant.

6

7 2. A composition comprising 40 wt % to 99.5 wt % of a member selected
8 from the group consisting of cellulose acylate, cellulose diacylate, cellulose
9 triacylate and ethylcellulose; 0.5 wt % to 60 wt % of an amphiphilic surfactant,
10 and an organic solvent wherein the cellulose member and the amphiphilic
11 surfactant exhibiting a solubility.

12

13 3. A composition comprising 40 wt % to 99.5 wt % of a member selected
14 from the group consisting of a cellulose acetate, a cellulose diacetate, a
15 cellulose triacetate, and ethyl cellulose; 0.5 wt % to 60 % of an amphiphilic
16 surfactant; which composition when coated onto a therapeutic drug
17 composition provides a dosage form for administering the drug over time.

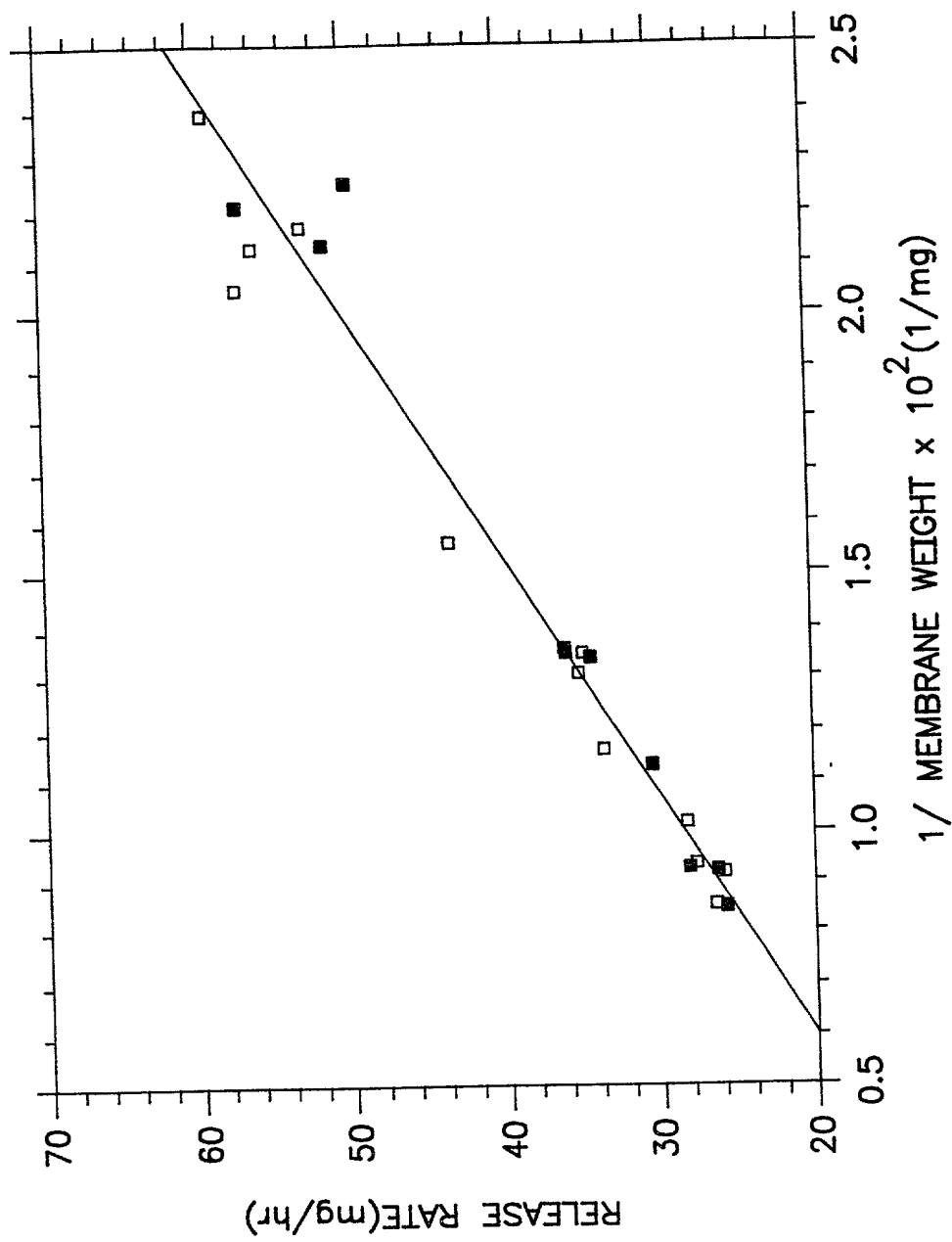
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19 4. A dosage form comprising: (1) a composition comprising a dose of
20 drug; (2) a composition comprising a polymer and an amphiphilic surfactant
21 that surrounds (1); and wherein the dosage form is characterized by : (3) a
22 solvent exhibiting common solubility for the polymer and the surfactant for
23 surrounding (1) with (2) to provide the dosage form.

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FIG. 1



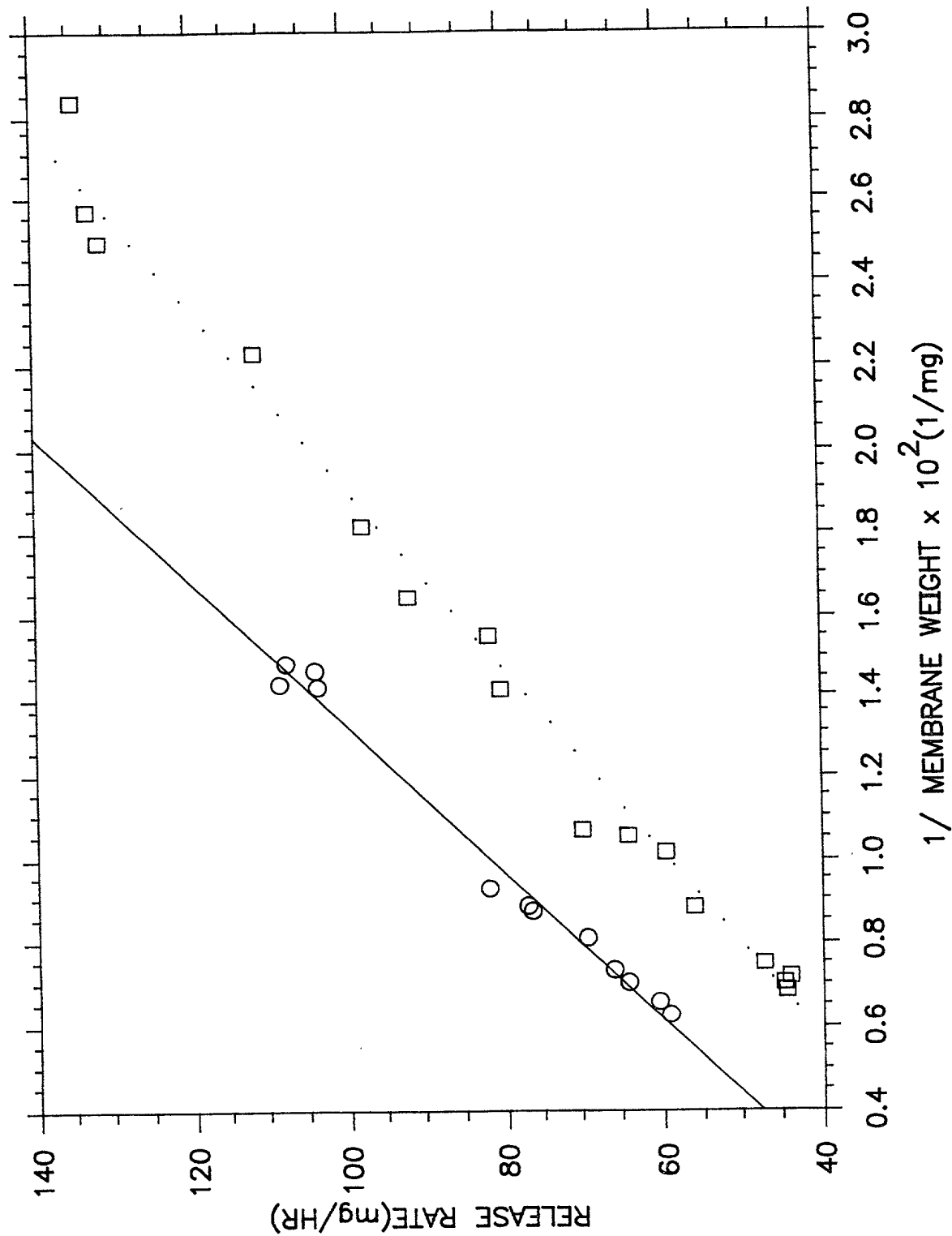


FIG. 2

FIG. 3

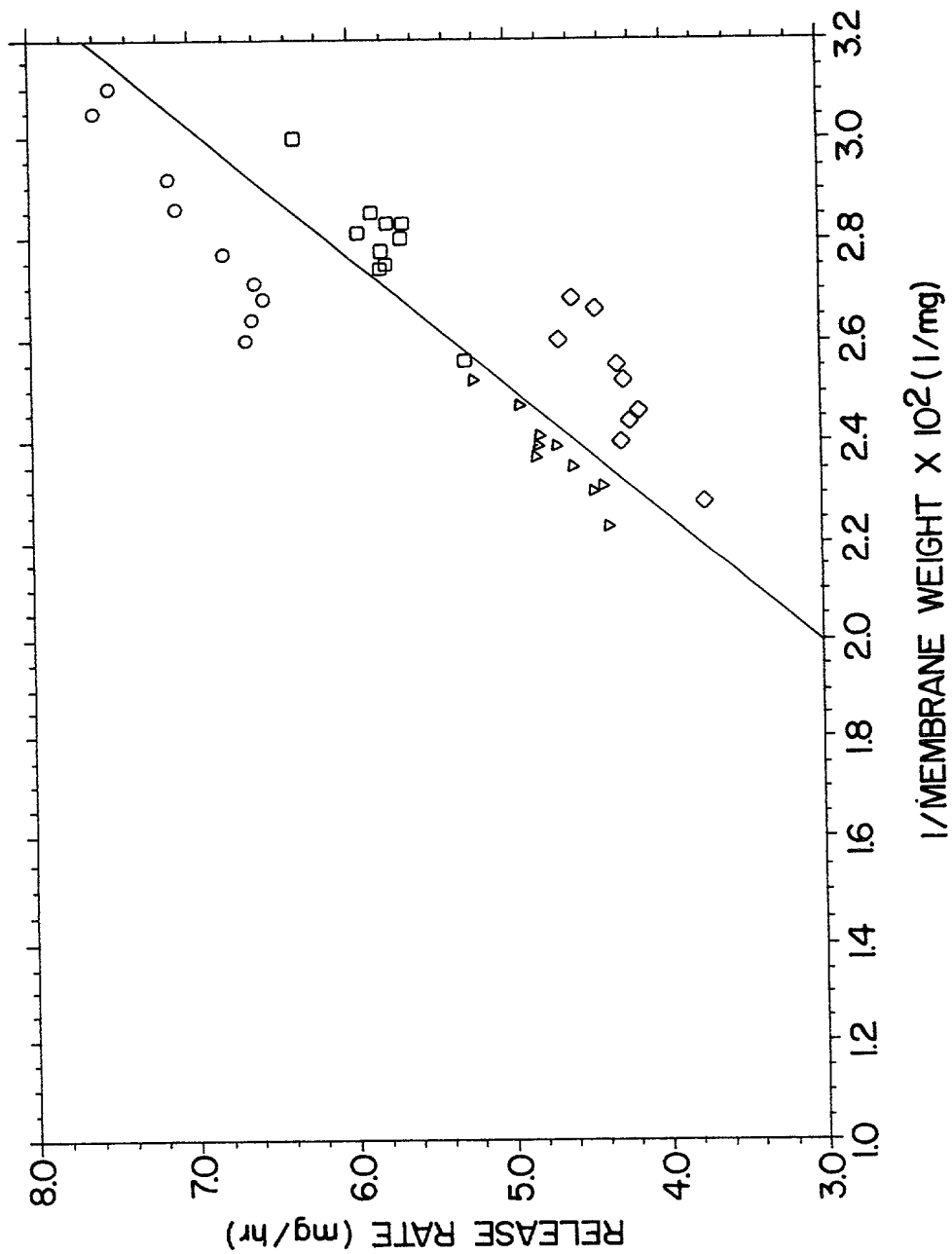


FIG. 4

Docket No.
ARC 2702 R1

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

PHARMACEUTICAL COATING COMPOSITION AND METHOD OF USE

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on _____ as United States Application No. or PCT International Application Number _____ and was amended on _____

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

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I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

60/058,264

09/09/97

(Application Serial No.)

(Filing Date)

(Application Serial No.)

(Filing Date)

(Application Serial No.)

(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)

(Filing Date)

(Status)
(patented, pending, abandoned)

(Application Serial No.)

(Filing Date)

(Status)
(patented, pending, abandoned)

(Application Serial No.)

(Filing Date)

(Status)
(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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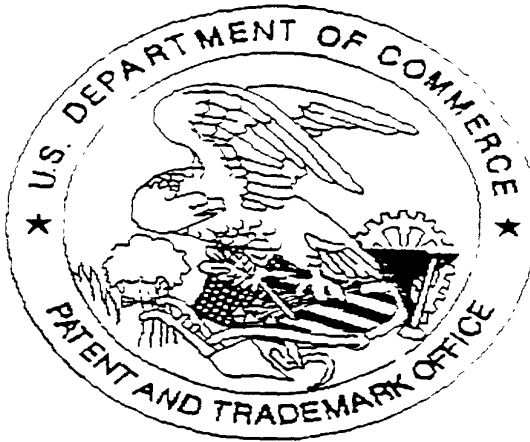
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